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A REVIEW ON DAPAGLIFLOZIN FOR THE TREATMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Diabetes is a complex and chronic illness characterized by hyperglycemia. Anti-diabetic agents become less effective overtime and are often associated with undesirable effects. Improvement in glycemic control through inhibition of sodium glucose co-transporter (SGLT-2) inhibitors is an attractive, insulin independent target for increasing glucose excretion via urine, resulting in reduction of glycated hemoglobin, fasting and postprandial plasma glucose in patients with Type 2 Diabetes Mellitus (T2DM). SGLT2 inhibitor dapagliflozin provides an alternative and an addition to existing therapies for the treatment of patients with T2DM. It is a stable, competitive, reversible and highly selective inhibitor of SGLT-2 with an insulin-independent mechanism of action. It has potential to reduce hyperglycemia by inhibiting glucose reabsorption in kidney. Dapagliflozin when used as monotherapy and as add-on with metformin, glimepiride, sitagliptin or insulin improved glycemic control and resulted in statistically significant ($p<0.0001$) reductions in HbA_{1c} compared to placebo. In clinical trials incidence of adverse events after single and multiple doses of dapagliflozin did not appear to be dose-related. Multiple oral doses of dapagliflozin either alone or with metformin were found to be safe and well tolerated. In randomized controlled trials hyperglycemia occurred in similar proportion of patients in dapagliflozin and placebo group. Urinary tract and genital infections were reported more in dapagliflozin treated patients than placebo. Dapagliflozin was not associated with an increase in cardiovascular risk in T2DM patients. Dapagliflozin with its unique and complimentary action either alone or in combination with other antidiabetic drugs provide an important option for the management of T2DM.

Key Words:- Dapagliflozin, SGLT2 inhibitor, Diabetes, Hyperglycemia, Kidney.

INTRODUCTION

Diabetes is a complex and chronic metabolic disease characterized by hyperglycemia due to defects in the secretion and action of insulin (Hinnen D, 2013). Diabetes continues to be a global health care problem (Freeman JS, 2013; Kipnes M, 2009; Ghosh RK *et al*., 2012). Around 347 million people worldwide have diabetes. More than 80% of diabetes deaths occur in low- and middle-income countries. WHO projects that diabetes will be the 7th leading cause of death in 2030 (World Health Organization, 2013). Diabetes is mainly classified as Type 1 diabetes and Type 2 diabetes. Type 1 diabetes (known as insulin-dependent, juvenile or childhood-onset) is characterized by deficient insulin production and requires daily administration of insulin. Type 2 diabetes (formerly called non-insulin-dependent or adult-onset) results from the body's ineffective use of insulin (American Diabetes Association, 2013). Type 2 diabetes mellitus (T2DM) comprises 90% of people with diabetes around the world, and is largely the result of excess body weight and physical inactivity (World Health Organization, 2013). It is associated with the development of a number of devastating macrovascular and microvascular complications, including heart disease,

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stroke, retinopathy, neuropathy, and nephropathy (Hinnen D 2013; Kipnes M, 2009; Woo VC, 2009).

Lifestyle modification, including nutritional therapy and physical activity, should continue to be emphasized while pharmacotherapy is being used (Woo VC, 2009). Current agents have been shown to modestly improve glycemia and in some cases prevent complications of diabetes, but they become less effective over time and are often accompanied by undesirable adverse effects (Shah NK *et al*., 2012; Katsiki N *et al*., 2010). Epidemiological studies suggest that a substantial proportion of patients does not achieve glycemic goals and so suffers from the risk of chronic complications (Salvatore T *et al*., 2011). In the United States > 40% of adults with diabetes fail to achieve target glycated hemoglobin levels (Freeman JS, 2013).

Antidiabetic drug classes vary with respect to their mechanisms of action, glucose-lowering potential, safety and tolerability profiles. Antidiabetic drug classes include agents that depend on the presence or action of insulin for their therapeutic effect and have significant limitations (Freeman JS, 2013; Bhartia M *et al*., 2011. When selecting an oral antidiabetic agent several factors should be considered, such as the effects on glucose, lipids, adverse reaction profile and patient's body weight. Pharmacologic therapy should be tailored to the goals and needs of each individual patient based on patient-specific factors to optimize blood glucose control. Currently, a variety of medications such as sulfonylureas, biguanides, thiazolidinediones, meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, alpha-glucosidase inhibitors and sodium glucose co-tranporter (SGLT-2) inhibitors are available to treat T2DM (Ketz J, 2001).

Despite the availability of numerous treatment options, antidiabetic drugs are not adequately effective in maintaining long-term glycemic control in most patients, even when used in combination (Hinnen D, 2013; Ghosh RK, 2012). Hence, there is a need for newer agents that can be used alone or in combination with currently approved medications to lower blood glucose levels with unique mechanisms of action (Freeman JS, 2013; Shah NK *et al*., 2012). Drugs which inhibit the sodium glucose co-transporter (SGLT-2 inhibitors) in the renal tubules, represent a novel class of drugs (Bhartia M *et al.*, 2011). SGLT-2 increases urinary excretion of glucose and lower plasma glucose levels (Ghosh RK, 2012; Plosker GL, 2012; Prescribing Information of Forxiga, 2012).

Sodium-glucose co-transporter (SGLT)

Sodium-glucose Co-transporters encompass family of membrane proteins, responsible for transport of glucose, amino acids, vitamins, ions and osmolytes across the brush-border membrane of proximal renal tubules as well as the intestinal epithelium. Two most well known members of SGLT family are SGLT-1 and SGLT-2 (Singhal M *et al*., 2012). SGLT-1 is primarily expressed in the small intestine but is also found in the trachea, kidney and heart. SGLT-2 is a high capacity, low-affinity transporter expressed chiefly in the kidney. They contribute to renal glucose reabsorption and most of renal glucose (about 90%) is reabsorbed by SGLT-2 located in the proximal renal tubule (Kipnes M, 2009; Salvatore T *et al*., 2011; Neumiller JJ *et al*., 2010; List JF, Whaley JM, 2011; Jabbour SA, Goldstein BJ, 2008). Selective inhibition of SGLT-2 in the proximal tubule increases urinary glucose excretion thereby reducing plasma glucose levels in an insulin-independent manner, which may present a novel therapeutic approach (List JF, Whaley JM, 2011; Vallon V, Sharma K, 2010; Wan HX, Shen JK, 2012; Ho LT *et al*., 2011; Simonyi G, 2012; Davidson J *et al*., 2011). SGLT-2 inhibitors provide an insulin-independent means to reduce the hyperglycemia that is the hallmark of T2DM (Washburn WN, 2012). In clinical trials, SGLT-2 inhibitors have shown significant reduction in HbA_{1C} and body weight in patients with T2DM. This lowering in body weight may reduce systolic blood pressure (Vallon V, Sharma K, 2010). SGLT-2 inhibitors may provide an alternative or an addition therapy for the treatment of patients with T2DM (Freeman JS, 2013).

Dapagliflozin is the first SGLT-2 inhibitor developed by AstraZeneca and Bristol-Myers Squibb Company and has been approved by the European Commission on 14th November 2012. It has also recently been approved by USFDA on 8th January 2014 for the treatment of T2DM. Canagliflozin is another SGLT-2 inhibitor developed by Johnson & Johnson which has gained approval by the USFDA on March 2013. Empagliflozin, Ipragliflozin, Luseogliflozin, Tofogliflozin hydrate and Ertugliflozin are other SGLT-2 inhibitors in the clinical development (Cormac S, 2012). Dapagliflozin is a first-in-class SGLT-2 inhibitor approved for treatment of T2DM and is the focus of this review.

Dapagliflozin

Dapagliflozin, a SGLT-2 inhibitor, unlike oral antidiabetic drugs has the potential to reduce hyperglycemia independently of insulin by inhibiting glucose reabsorption in the kidney (Kipnes M, 2009; Woo VC, 2009). Dapagliflozin has shown to be a potential therapeutic agent in the management of T2DM (Anderson SL, Marrs JC, 2012). It also provides complementary therapy via its unique mechanism of action when used in combination with other antidiabetic drugs (Plosker GL, 2013).

Mechanism of action

Dapagliflozin is a selective, competitive inhibitor of SGLT-2. Selectively and reversible blockage of SGLT-2 receptor, prevents reabsorption of glucose at the renal proximal tubule (Shah NK et al., 2012; Demaris KM, White JR, 2013) that leads to increase in renal glucose excretion via the urine, resulting in reduction of glycated hemoglobin, fasting plasma glucose and postprandial plasma glucose in patients with T2DM (Salvatore T *et al.*, 2011; Gerich JE, Bastien A, 2011; Rosak C, Forst T, 2012). Independent of pancreatic β cell function or modulation of insulin sensitivity, it promotes glucosuria and direct lowering of plasma glucose concentrations (Demaris KM, White JR, 2013; Rosak C, Forst T, 2012) (Figure 1).

Pharmacodynamics

Dapagliflozin has demonstrated dose-dependent glucosuria in healthy subjects (Kasichayanula S *et al.*, 2011; Komoroski B *et al.*, 2009a). and in patients with T2DM Kasichayanula S *et al.*, 2011; Zhang L *et al.*, 2010; Komoroski B *et al.*, 2009b; List JF *et al.*, 2009). In healthy subjects the mean cumulative amounts of urinary glucose excretion over 24 h postdose were 7.45, 24.4, 28.5 and 32.2 g respectively following administration of 2.5, 10, 20 and 50 mg of dapagliflozin (Kasichayanula S *et al.*, 2011). Doses on the order of 20-50 mg maintained a close-to-maximal rate of glucose excretion of ~ 3g/h or 70g/day by day 14. Cumulative amounts of glucose excreted over 24h on day 1 and day 14 translated to ~20-30% and ~16-50% inhibition of renal glucose reabsorption respectively (Komoroski B *et al.*, 2009a; Komoroski B *et al.*, 2009b). In subjects with T2DM, comparable glucose excretion was seen on day 1 and day 14, where cumulative amounts of urinary glucose excretion over 24 h were 6.8, 41.6, 71.4, and 73.0 g, following once daily administration of placebo, 2.5, 10 and 20 mg of dapagliflozin treatment respectively (Kasichayanula S *et al.*, 2011). At week 12, all dapagliflozin treatment groups had significant increases in urinary glucose excretion from baseline (Zhang L *et al.*, 2010). Total mean urinary glucose excreted per 24 h ranged from 52 to 85 g. All the treated groups demonstrated significant glycemic improvements versus placebo (Δ HbA_{1C} -0.55 to -0.90% and Δ FPG -16 to -31 mg/dl). Near-maximal effect on PPG reductions were also observed (Zhang L *et al.*, 2010; List JF *et al.*, 2009). Dapagliflozin also exhibited a diuretic effect, with small dose-dependent increases in urine volume equivalent to ~ 0.3–1.5 voids/day, small increases in blood urea nitrogen (BUN) and hematocrit (List JF *et al.*, 2009). In a pooled analysis of 12 placebo-controlled studies, treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of -4.4 mmHg and diastolic blood pressure of -2.1 mmHg versus -0.9 mmHg and -0.5 mmHg for placebo at Week 24 (Summary of Product Characteristics of Forxiga, 2012).

Pharmacokinetics

Dapagliflozin pharmacokinetics has been studied in healthy subjects as well as subjects with T2DM and subjects with renal or hepatic impairment (Public Assessment Report of Forxiga, 2012). Dapagliflozin is rapidly absorbed after oral administration and attain maximum peak plasma concentrations within 2 h (Komoroski B *et al.*, 2009a; Kasichayanula S *et al.*, 2013). Dose-proportional systemic exposure has been observed over a wide dose range (0.1-500 mg) with an oral bioavailability of 78 % (ranging from 70 to 90%) (Public Assessment Report of Forxiga, 2012). It has extensive extravascular distribution (mean volume of distribution of 118 L) and protein binding is approximately 91%. Dapagliflozin metabolism occurs predominantly in the liver and kidneys by uridine diphosphate-glucuronosyltransferase-1A9 (UGT1A9) to the major metabolite dapagliflozin 3-O-glucuronide (Kasichayanula S *et al.*, 2011; Kasichayanula S *et al.*, 2013). It is not appreciably cleared by renal excretion (<2 % of dose is recovered in urine as parent). The half-life for orally administered dapagliflozin 10 mg is 12.9 h (Kasichayanula S *et al.*, 2013). Dapagliflozin 3-O-glucuronide elimination occurs mainly via renal excretion, with 61 % of a dapagliflozin dose being recovered as this metabolite in urine (Plosker GL, 2012; Macha S *et al.*, 2012; Prescribing Information of INVOKANA, 2013; Prescribing Information of INVOKANA, 2013). No clinically relevant differences were observed in dapagliflozin exposure with respect to age, race, sex, body weight, food or presence of T2DM (Kasichayanula S *et al.*, 2013). Patients with severe renal or hepatic impairment show higher systemic exposure to dapagliflozin (Kasichayanula S *et al.*, 2013, 2012). Pharmacokinetics in the pediatric population has not been studied (Summary of Product Characteristics of Forxiga, 2012). Dapagliflozin showed predictable dose-proportional PK parameters in both healthy and T2DM Japanese subjects (Kasichayanula S *et al.*, 2011).

Drug interactions

Dapagliflozin has a low propensity for pharmacokinetic drug interactions. No clinically significant pharmacokinetic interactions were demonstrated between dapagliflozin and the oral antidiabetic drugs metformin, pioglitazone, sitagliptin, glimepiride or voglibose in healthy volunteers (Plosker GL, 2012; Kasichayanula S *et al.*, 2011; Public

Assessment Report of (Forxiga, 2012). Dapagliflozin had no effect on the pharmacokinetics of simvastatin, valsartan, hydrochlorothiazide, bumetanide (Summary of Product Characteristics of Forxiga, 2012) digoxin and warfarin (Bailey CJ *et al.*, 2012). Modulators of UGT1A9 could increase or decrease systematic exposure (AUC) of dapagliflozin (Kasichayanula S *et al.*, 2013). Modest changes in dapagliflozin exposure were seen with rifampin and mefenamic acid but with no clinically meaningful effect on 24-hour urinary glucose excretion (Kasichayanula S *et al.*, 2013). No clinically relevant effect with carbamazepine, phenytoin, phenobarbital is expected (Summary of Product Characteristics of Forxiga, 2012). The pharmacodynamics of warfarin were also unaffected by dapagliflozin (Kasichayanula S *et al.*, 2012). Some pharmacodynamic interactions with dapagliflozin are of clinical relavance, notably the potential for volume depletion when combined with loop diuretics and an increased risk of hypoglycemia when combined with insulin or insulin secretagogues e.g. sulfonylureas (Plosker GL, 2012).

Efficacy

The efficacy of dapagliflozin has been studied in various randomized, placebo and active controlled clinical trials either as monotherapy or as an add-on therapy in patients with inadequate glycaemic control with insulin, metformin, pioglitazone, glimepiride and sitagliptin.

Dapagliflozin Monotherapy Trials

In randomized, double blind clinical trials, dapagliflozin were evaluated as monotherapy with dose range from 1 mg to 100 mg per day for duration ranges from 2 weeks to 24 weeks. In these monotherapy clinical trials, dapagliflozin was compared with placebo. Significant reduction in HbA_{1C} from baseline has been reported with dapagliflozin 5 mg (-0.37 to -0.82%) and dapagliflozin 10 mg (-0.33 to 0.89%) vs. placebo (0.35 to -0.23%). Also significant reduction in *FPG from baseline value has been reported with dapagliflozin 5 mg (-0.47 to -1.58%) and dapagliflozin 10 mg (-0.76 to -1.77%) vs. placebo (0.5 to -0.33%). Proportion of patients achieving HbA_{1C} <7 % in dapagliflozin monotherapy trials ranged from 5.2 to 49.1% for 5 mg group and 9.6 to 52% 10 mg group respectively. Significant change in total body weight also ranged from -2.8 to -2.13kg with dapagliflozin 5 mg and -2.22 to -3.2kg with dapagliflozin 10 mg respectively. In all these trials it was observed that fasting plasma glucose and HbA_{1C} level decreases with increasing the dose of dapagliflozin (Table 1, Figure 2 and 3).

Dapagliflozin Combination Trials

Many randomized controlled trials have been reported with dapagliflozin in combination with metformin, insulin, pioglitazone, glimepiride and sitagliptin (Table 2).

Combination with Metformin

In randomized double blind efficacy clinical trials dapagliflozin in combination with metformin was evaluated at doses ranges from 2.5-10 mg/day with duration from 24-52 weeks. Dapagliflozin plus metformin treatment resulted in significant improvement in glycaemic control, HbA_{1C} decrease from baseline ranged from -0.65 to -2.05% for 5 mg and -0.59 to -1.98% for 10 mg group and FPG decrease from baseline was -1.4 to -3.39 mmol/l for 5 mg and -0.52 to -3.39 for 10 mg group. Proportion of patients achieving HbA_{1C} <7 % ranged from 37.5-52.4% in dapagliflozin 5 mg group and 28.1-46.6% in dapagliflozin 10 mg group. Change in total body weight was -2.66 to -3.2kg and -1.44 to -4.39kg with dapagliflozin 5 mg and 10 mg respectively.

Combination with Insulin

Randomized double blind efficacy clinical trials of dapagliflozin at doses ranges from 2.5-50 mg/day in combination with insulin were reported with duration from 12-24 weeks. In these trials dapagliflozin plus insulin treatment resulted in significant improvement in glycaemic control, HbA_{1C} decrease from baseline ranged from -0.61 to -0.96% and FPG decrease from baseline ranged from -0.13 to -1.1 mmol/l. Change in total body weight was -0.92 to -4.5kg.

Combination with Pioglitazone

A randomized double blind 24 weeks efficacy clinical trial of dapagliflozin at doses ranges from 5-10 mg/day in combination with pioglitazone was reported. Dapagliflozin plus pioglitazone treatment resulted in improvement in glycaemic control, HbA_{1C} decrease from baseline ranged from -0.82 to -0.97% and FPG decrease from baseline ranged from -1.38 to -1.64 mmol/l respectively. A greater reduction in mean change from baseline in PPG was also reported with dapagliflozin plus pioglitazone (-3.35 to -0.49 mmol/L) than with placebo plus pioglitazone (-1.41 mmol/L) (Rosenstock J *et al*., 2012). Change in total body weight was 0.09 to -0.14 kg.

Combination with Glimepiride

A randomized double blind 24 weeks efficacy clinical trial of dapagliflozin at doses ranges from 5-10 mg/day in combination with glimepiride was reported. HbA_{1C} decrease from baseline was from -0.58 to -0.82%

and FPG decrease from baseline ranged from -0.93 to - ranged from 30-31 %. Change in total body weight was -1.18 to -2.26kg.

Combination plus Sitagliptin and Metformin

A randomized double blind 24 weeks efficacy clinical trial of dapagliflozin at doses ranges from 5-10 mg/day in combination with sitagliptin and metformin was reported. Dapagliflozin plus sitagliptin and metformin combination treatment resulted in improvement in glycaemic control, HbA_{1C} decrease from baseline was -0.45% and FPG decrease from baseline was -1.33 mmol/l. Change in total body weight was -2.14 kg.

Safety

The information on safety and tolerability of dapagliflozin has been assessed in randomized multicentre controlled clinical trials with a cumulative patient's exposure of more than 9000 subjects. The incidence of adverse events (AEs) after single and multiple doses of dapagliflozin did not appear to be dose-related in clinical trials and were found to be safe and well tolerated (Table 3). A total of 240 serious adverse events, 17 deaths and around 200 discontinuations due to drug-related adverse events were reported in these clinical studies. A total of 23 cases of cancer have been reported which include 9 cases of breast cancer, 9 cases of bladder cancer, 2 cases of prostate cancer, 2 cases of colon cancer and 1 case of rectal cancer. One subject receiving dapagliflozin developed acute hepatitis with diagnoses of drug induced hepatitis and/or autoimmune hepatitis (FDA Briefing Document, 2011). Other serious adverse events includes transient ischaemic attack, stroke, complex ventricular arrhythmia, worsening of coronary artery disease, pulmonary embolism, oesophageal variceal haemorrhage, chronic lymphatic leukaemia, gastroduodenitis, convulsion, transient global amnesia, spinal osteoarthritis, decreased calculated creatinine clearance, tuberculosis and pneumonia.

1.58 mmol/l. Proportion of patients achieving HbA_{1C} <7 %

A meta-analysis of cardiovascular events confirmed that dapagliflozin was not associated with an increase in cardiovascular risk in patients with T2DM (Summary of Product Characteristics of Forxiga, 2012). In randomized placebo controlled study dapagliflozin had no effect on markers of bone formation and resorption or bone mineral density (BMD) after 50 weeks of treatment in both male and post-menopausal female T2DM patients (Ljunggren Ö *et al*., 2012).The most frequent treatment emergent AEs were typically gastrointestinal in nature and were more in subjects taking metformin, insulin, glimepiride and pioglitazone concomitantly (Komoroski B *et al*., 2009a). Dapagliflozin had a low propensity for hypoglycaemia (Public Assessment Report of Forxiga, 2012) and was similar to placebo in randomized placebo controlled phase III studies of 24 week duration. There were no major episodes of hypoglycaemia reported in these studies (Bailey CJ *et al.*, 2012; Ferrannini E *et al.*, 2010).Other commonly reported adverse events include nasopharyngitis, headache, upper respiratory tract infection, hypoglycaemia, urinary tract infection and genital tract infection. Events suggestive of genital or urinary tract infections are considered as events of special interest because they appear to be related to the mechanism of action of dapagliflozin, which promotes glucosuria (Plosker GL, 2012). In dapagliflozin placebo-controlled monotherapy trials, the overall proportion of subjects with events suggestive of genital infection events and urinary tract infection was higher in dapagliflozin-treated subjects than placebo-treated subjects. The most commonly reported genital infections were vulvovaginal mycotic infection, vaginal infection, vulvovaginal pruritus/candidiasis, balanitis, and mycotic genital infection. Urinary tract infections reported were pollakiuria, cystitis, dysuria and pyelonephritis. Genital and urinary tract infections were reported to be more frequent in females than in males (Figure 4 and 5) (Public Assessment Report of Forxiga, 2012).

Table 1. Dapagliflozin Monotherapy Trials

Reference	Study design (duration)	Intervention	N	FPG (mmol/l)		p value	HbA_{1C} (%)		p value	Proportion of patients achieving HbA_{1C} <7 %
				Baseline	Change from baseline		Baseline	Change from baseline		
Clinicaltrials.gov [NCT00972244]*	MC, R, DB, PC, PG, Phase 2 (12weeks)	PL	54	-	0.5	<0.0001	8.12	0.35	<0.0001	1.9%
		DAPA 1 mg	59	-	-0.92		8.10	-0.12		1.7 %
		DAPA 2.5 mg	56	-	-1.10		7.92	-0.10		9.3%
		DAPA 5 mg	58	-	-1.3		8.05	-0.37		5.2%
		DAPA 10	52	-	-1.77		8.18	-0.44		9.6%

Reference	Study design (duration)	Intervention	N	FPG (mmol/l)		p value	HbA_{1C} (%)		p value	Proportion of patients achieving HbA_{1C} <7 %
				Baseline	Change from baseline		Baseline	Change from baseline		
		mg								
Bailey CJ *et al*., 2012	R, DB,PC, Phase 3 (24weeks)	PL	68	8.97	0.23		7.80	0.02		34.6 %
		DAPA 1mg	72	8.64	-0.61	<0.001	7.80	-0.68	<0.0001	53.6 %
		DAPA 2.5mg	74	8.87	-1.20	<0.0001	8.07	-0.72	<0.0001	43.4 %
		DAPA 5mg	68	8.72	-1.58	<0.0001	7.92	-0.82	<0.0001	49.1 %
Ferrannini E, 2010	R, DB, PC, Phase 3 (24weeks)	PL	75	8.88	-0.22	-	7.84	-0.23	-	32%
		DAPA 2.5mg	65	9.1	-0.84	-	7.92	-0.58	-	41%
		DAPA 5mg	64	9.01	-1.3	<0.001	7.86	-0.77	<0.001	44%
		DAPA 10 mg	70	9.25	-1.6	<0.0001	8.01	-0.89	<0.0001	51%
List JF, 2009	R, PC (12weeks)	PL	54	8.33	-0.33	-	7.9	-0.18	-	32%
		DAPA 2.5 mg	59	8.05	-0.88	0.001	7.6	-0.71	<0.001	46%
		DAPA 5 mg	58	8.5	-1.05	0.0001	8.0	-0.72	<0.001	40%
		DAPA 10 mg	47	8.22	-1.16	0.0001	8.0	-0.85	<0.001	52%
		DAPA 20 mg	59	8.27	-1.33	<0.001	7.7	-0.55	0.007	46%
		DAPA 50 mg	56	8.5	-1.72	<0.001	7.8	-0.90	<0.001	59%
		MET	56	7.9	-1	-	7.6	-0.73	-	54%
Clinicaltrials.gov [NCT01294423]*	R, DB, PC, PG Phase 3 (24weeks)	PL	87	7.75	0.32	-	7.50	-0.06	-	-
		DAPA 5 mg	86	7.63	-0.47	<0.0001	7.50	-0.41	<0.0001	-
		DAPA10 mg	88	7.71	-0.76	<0.0001	7.46	-0.45	<0.0001	-
Clinicaltrials.gov [NCT01042977]*	R, DB, PC, Phase 3 (24weeks)	PL	482	-	-	-	8.08	0.07	-	
		DAPA 10 mg	480	-	-	-	8.04	-0.33	<0.0001	-
Clinicaltrials.gov [NCT01031680]*	MC, R, DB, PC, Phase 3 (24weeks)	PL	459	-	-	-	8.08	0.08	-	-
		DAPA 10 mg	455	-	-	-	8.18	-0.38	<0.0001	-
Komoroski B *et al*., 2009b	R, DB, PC, Phase 2 (2 weeks)	PL	8	-	-	-	-	-	-	-
		DAPA 5 mg	11	-	-1.04	-	-	-	-	-
		DAPA25 mg	12	-	-1.6	-	-	-	-	-
		DAPA100 mg	16	-	-2.5	-	-	-	-	-

DAPA-Dapagliflozin, MET- Metformin, PL-Parallel group, PL-Placebo, R-Randomized, DB-Double blind, PC-Placebo controlled, FPG-Fasting Plasma Glucose, HbA_{1C}-Glycated haemoglobin. *As per results published on clinicaltrials.gov.

Table 2. Dapagliflozin Combination Trials

Reference	Study design (duration)	Intervention	N	FPG (mmol/l)		p value	HbA_{1C} (%)		p value	Proportion of patients achieving HbA_1c <7 %
				Baseline	Change from baseline		Baseline	Change from baseline		

Reference	Study design (duration)	Intervention	N	FPG (mmol/l)		p value	HbA_{1C} (%)		p value	Proportion of patients achieving HbA_1c <7 %
				Baseline	Change from baseline		Baseline	Change from baseline		
Combination with Metformin										
Henry RR *et al*., 2012	Study 1 R, DB, (24 week)	MET + PL	201	10.92	-1.86		9.14	-1.35		34.6%
		DAPA 5mg + PL	203	10.59	-2.33		9.14	-1.19		22.5%
		DAPA 5mg + MET	194	10.73	-3.39	<0.0001	9.21	-2.05	<0.0001	52.4%
	Study 2 R, DB, (24 week)	MET+PL	208	10.54	-1.93		9.03	-1.44		35.2%
		DAPA 10mg + PL	219	10.96	-2.58		9.03	-1.45		31.7%
		DAPA 10mg + MET	211	10.52	-3.35	<0.0001	9.10	-1.98	<0.0001	46.6%
Bailey CJ *et al*., 2010	R, DB, PC, Phase 3, PG (24weeks)	PL+MET	137	9.19	-0.33		8.11	-0.30		25.9%
		DAPA 2.5mg+MET	137	8.96	-0.99	<0.001	7.99	-0.67	<0.001	33%
		DAPA 5mg+MET	137	9.39	-1.19	<0.0001	8.17	-0.70	<0.0001	37.5%
		DAPA 10 mg+MET	135	8.66	-1.30	<0.0001	7.92	-0.84	<0.0001	40.6%
Nauck MA *et al*., 2011	DB, MC, (52 week)	MET + GLIP (≤ 20 mg)	408	7.74	-0.52	<0.0001	-	-		-
		MET + DAPA (≤ 10 mg)	406	7.69	-0.52		-	-		-
Ljunggren O *et al*., 2012	MC, R, DB, PC, PG (50weeks)	PL + MET	91	8.30	0.13	<0.0001	7.16	0.02	-	-
		DAPA 10 mg + MET	89	8.21	-0.82		7.19	-0.38	-	-
Clinicaltrials.gov [NCT01217892]*	MC, R, DB, PC, Phase 3	PL + MET	101	8.76	-0.5	-	7.94	-0.30	-	21.4%
		DAPA 2.5 mg +MET	100	8.51	-1.15	<0.001	7.77	-0.52	<0.01	33.6%
		DAPA 5 mg +MET	99	8.62	-1.4	<0.0001	7.78	-0.65	<0.0001	38.2%
		DAPA 10 mg +MET	99	8.62	-1.13	-	7.71	-0.59	-	28.1%
Combination with Insulin										
Wilding J, 2009	R, DB, PC (12 weeks)	PL + INS	24	9.26	0.98	-	8.3	0.09	-	4.2%
		DAPA 10 mg + INS	23	8.65	0.13	-	8.4	-0.61	-	12.5%
		DAPA 20 mg + INS	24	8.77	-0.53	-	8.5	-0.69	-	4.2%
Wilding J, 2012	R, DB, PC, MC (24 weeks)	PL + INS	193	9.5	-		8.47	-0.39		-
		DAPA 2.5mg + INS	202	10	-0.65	<0.001	8.46	-0.79	<0.001	-
		DAPA 5mg + INS	211	10.3	-1.1		8.62	-0.89		-
		DAPA 10 mg + INS	194	9.6	-1.1		8.57	-0.96		-
Combination with Pioglitazone										
Rosenstock *et al*., 2012	R, DB, PC, MC	PL+PIO	139	8.92	-0.31	<0.0001	8.34	-0.42	-	-

Reference	Study design (duration)	Intervention	N	FPG (mmol/l)		p value	HbA_{1C} (%)		p value	Proportion of patients achieving HbA_1c <7 %
				Baseline	Change from baseline		Baseline	Change from baseline		
	(24weeks)	DAPA 5mg+PIO	141	9.36	-1.38	<0.01	8.40	-0.82	<0.001	-
		DAPA 10mg+PIO	140	9.15	-1.64	<0.0001	8.37	-0.97	<0.0001	-
Combination with Sitagliptin and/or Metformin										
Clinicaltrials.gov [NCT00984867]*	R, DB, PC, PG,MC Phase 3 (24weeks)	PL+SITA ±MET	224	9.05	0.21		7.97	0.04		-
		DAPA 10mg+SITA ±MET	223	9.01	-1.33	<0.0001	7.90	-0.45	<0.0001	-
Combination with Glimepiride										
Strojek *et al*., 2011	R, DB, PC, MC, PG (24weeks)	PL+GLIM	143	9.6	-0.11		8.15	-0.13		13.0%
		DAPA 2.5mg+GLIM	154	9.6	-0.93		8.11	-0.58		-
		DAPA 5mg+GLIM	142	9.7	-1.18	<0.001	8.12	-0.63	<0.0001	30.3%
		DAPA 10 mg+GLIM	150	9.6	-1.58		8.07	-0.82		31.7%

DAPA-Dapagliflozin, MET-Metformin; PIO-Pioglitazone, GLIM-Glimepiride, INS-Insulin, SITA-sitagliptin, PL-Placebo; R-Randomized; DB-Double blind; PC-Placebo controlled; FPG-Fasting Plasma Glucose; HbA_{1C}-Glycated haemoglobin; MC-Multicentre; PG-Parallel group; *As per results published on clinicaltrials.gov.

Table 3. Summary of Common Adverse Events in Randomized Trials of Dapagliflozin and in Comparison with Other Oral Anti-diabetic Drugs

Reference	Study Design	Total Subjects (N)	Treatment Arm(n)	Headache n (%)	Nasopharyngitis n (%)	URTI n (%)	Hypoglycemia n (%)	UTI n (%)	Genital Infection n (%)
Bailey CJ *et al*., 2012	R, DB, PC, Phase 3 (24 weeks)	282	Placebo (68) DAPA 1 mg (72) DAPA 2.5 mg (74) DAPA 5 mg (68)	5(7.4) 5(6.9) 4(5.4) 2(2.9)	3(4.4) 5(6.9) 1(1.4) 2(2.9)	3(4.4) 1(1.4) 4(5.4) 2(2.9)	1(1.5) 0 0 1(1.4)	1(1.5) 3(4.2) 1(1.4) 2(2.9)	2(2.9) 1(1.4) 5(6.8) 2(2.9)
Rosenstock J *et al*., 2012	R, DB, PC, PG (24 weeks)	420	PL + PIO (139) DAPA 5mg + PIO (141) DAPA 10mg + PIO (140)	10(7.2) 3(2.1) 4(2.9)	7(5.0) 7(5.0) 11(7.9)	10(7.2) 10(7.1) 7(5.0)	1(0.7) 3(2.1) 0	11(7.9) 12(8.5) 7(5.0)	1(0.7) 8(5.7) 6(4.3)
Wilding JP *et al*., 2012	R, PC (24 weeks)	808	PL (193) DAPA2.5mg + INS (202) DAPA 5mg+ INS (211) DAPA10mg+INS (194)	15(7.6) 11(5.4) 14(6.6) 5(2.6)	23(11.7) 32(15.8) 35(16.5) 25(12.8)	12(6.1) 6(3.0) 8(3.8) 9(4.6)	2(1) 3(1.5) 2(0.9) 3(1.5)	8(4.1) 11(5.4) 16(7.5) 14(7.1)	5(2.5) 13(6.4) 21(9.9) 21(10.7)
Henry RR *et al*., 2012	R,DB (24 weeks)	Study 1(598)	MET+PL (201) DAPA 5mg+MET (194) DAPA 5mg+PL (203)	-	-	11(5.5) 10(5.2) 10(4.9)	0 5(2.6) 0	15(7.5) 15(7.7) 16(7.9)	4(2.0) 13(6.7) 14(6.9)
		Study 2(638)	MET+PL (208) DAPA 10mg	-	-	7(3.4) 7(3.3)	6(2.9) 7(3.3)	9(4.3) 16(7.6)	5(2.4) 18(8.5)

Reference	Study Design	Total Subjects (N)	Treatment Arm(n)	Headache n (%)	Nasopharyngitis n (%)	URTI n (%)	Hypoglycemia n (%)	UTI n (%)	Genital Infection n (%)
			+MET (211) DAPA 10mg +PL (219)			6(2.7)	2(0.9)	24(11)	28(12.8)
Nauck MA *et al*., 2011	DB, R (52 weeks)	814	GLIP+MET(≤20 mg) (408) DAPA+MET(≤10mg) (406)	21(5.2) 17(4.2)	43(10.6) 61(15.0)	24(5.9) 31(7.6)	0 3(0.7)	30(7.4) 17(4.2)	50(12.3) 11(2.7)
Strojek *et al*., 2011	R, DB, PC, PG (24 week)	597	PL + GLIM (143) DAPA2.5mg+GLIM (154) DAPA5mg+GLIM (142) DAPA10mg+GLIM (150)	-	4(2.7) 3(1.9) 8(5.5) 5(3.3)	4(2.7) 5(3.2) 6(4.1) 7(4.6)	7(4.8) 11(7.1) 10(6.9) 12(7.9)	5(3.4) 4(2.6) 4(2.8) 4(2.6)	1(0.7) 6(3.9) 9(6.2) 10(6.6)
Bailey CJ *et al*., 2010	DB,PG, PC Phase 3 (24 weeks)	546	PL+MET (137) DAPA 2.5 mg+MET (137) DAPA 5 mg+MET (137) DAPA 10 mg+MET (135)	6(4) 4(3) 10(7) 11(8)	11(8) 12(9) 4(3) 8(6)	10(7) 5(4) 4(3) 3(2)	4(3) 3(2) 5(4) 5(4)	11(8) 6(4) 10(7) 11(8)	7(5) 11(8) 18(13) 12(9)
Ferrannini E *et al*., 2010	DB, PG, PC, Phase 3 (24 weeks)	558	PL (74) DAPA 2.5 mg (65) DAPA 5 mg (64) DAPA 10 mg (70)	5(6.7) 5(7.7) 3(4.7) 4(5.7)	4(5.3) 7(10.8) 3(4.7) 2(2.9)	-	2(2.7) 1(1.5) 0 2(2.9)	3(4.0) 3(4.6) 8(12.5) 4(5.7)	1(1.3) 5(7.7) 5(7.8) 9(12.9)
Wilding JP *et al*., 2009	R, DB, PC, PG (24 weeks)	163	PL (24) DAPA 10 mg+INS (23) DAPA 20 mg+INS (24)	2(8.7) 3(12.5) 0	2(8.7) 2(8.3) 2(8.3)	2(8.7) 2(8.3) 1(4.2)	1(4.3) 0 0	0 1(4.2) 0	1(4.3) 0 0
List JF., 2009	R, PG, DB, PC (12 weeks)	440	PL (54) DAPA 2.5 mg (59) DAPA 5 mg (58) DAPA 10 mg (47) DAPA 20 mg (59) DAPA 50 mg (56) MET (56)	6(11) 4(7) 3(5) 2(4) 3(5) 1(2) 2(4)	-	-	2(4) 4(7) 6(10) 3(6) 4(7) 4(7) 5(9)	3(6) 3(5) 5(9) 5(11) 4(7) 4(7) 4(7)	3(5.6) 4(6.8) 6(10.3) 5(10.6) 10(16.9) 9(16.1) 6(10.7)
Komoroski B *et al*., 2009b	R, DB, PC, Phase 2 (2 weeks)	47	PL (8) DAPA 5 mg (11) DAPA 25 mg (12) DAPA 100 mg (16)	1(12.5) 0 1(8.3) 2(12.5)	-	-	0 1(9.1) 1(8.3) 0	-	-
Clinicaltrials.gov [NCT00984867]	R, DB, PC, PG, Phase 3 (24	447	PL + SITA ± MET DAPA 10 mg + SITA ± MET	-	14(6.19) 9(4)	-	-	-	-

Reference	Study Design	Total Subjects (N)	Treatment Arm(n)	Headache n (%)	Nasopharyngitis n (%)	URTI n (%)	Hypoglycemia n (%)	UTI n (%)	Genital Infection n (%)
*	weeks)								
Clinicaltrials.gov [NCT01294423] *	R, DB, PC, PG Phase 3 (24 weeks)	261	PL DAPA 5 mg DAPA 10 mg	-	9(10.34) 9(10.47) 15(17.05)	-	-	-	-
Clinicaltrials.gov [NCT01042977] *	R, DB, PC, Phase 3 (24 weeks)	962	PL DAPA 10 mg	-	26(5.38) 26(5.39)\	24(4.97) 15(3.11)	84(17.39) 101(21.1)	18(3.73) 27(5.6)	-
Clinicaltrials.gov [NCT01031680] *	MC, R, DB, PC, Phase 3 (24 weeks)	914	PL DAPA 10 mg	-	0 1(0.22)	-	0 1(0.22)	0 1(0.22)	-
Clinicaltrials.gov [NCT01294436] *	Open label (52 weeks)	728	DAPA 5/10 mg + any anti-diabetic drug DAPA 5/10 mg	-	116(479) 63(25.30)	-	-	-	-

DAPA-Dapagliflozin, MET-Metformin, PIO-Pioglitazone, GLIM-Glimepiride, INS-Insulin, PL-Placebo, R-Randomized, DB-Double blind, PC-Placebo controlled, MC-Multicentre, PG-Parallel group, *As per results published on clinicaltrials.gov.

Figure 1. Mechanism of action and clinical effects of sodium-glucose co-transporter 2 inhibitors

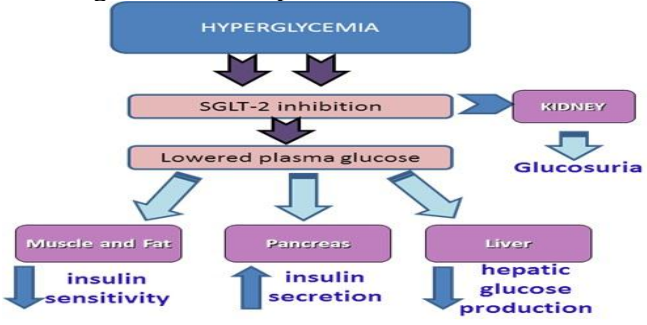


Figure 2. Decrease in Fasting Plasma Glucose Level

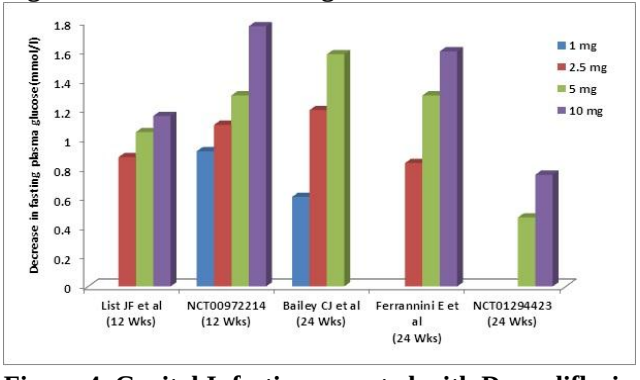


Figure 3. Decrease in HbA_{1C} Level

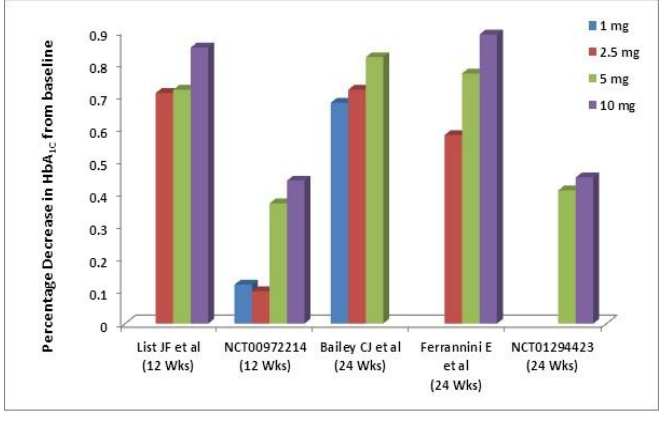


Figure 4. Genital Infection reported with Dapagliflozin Monotherapy

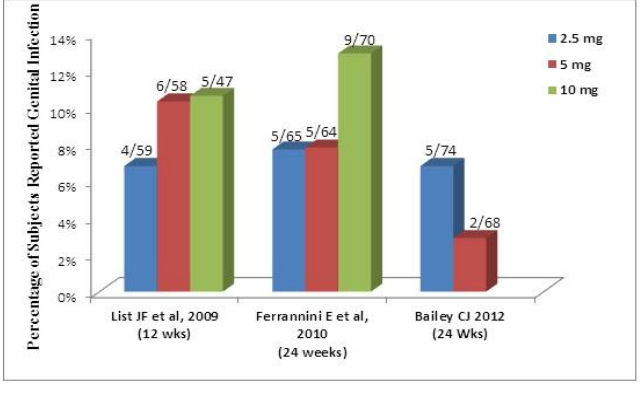
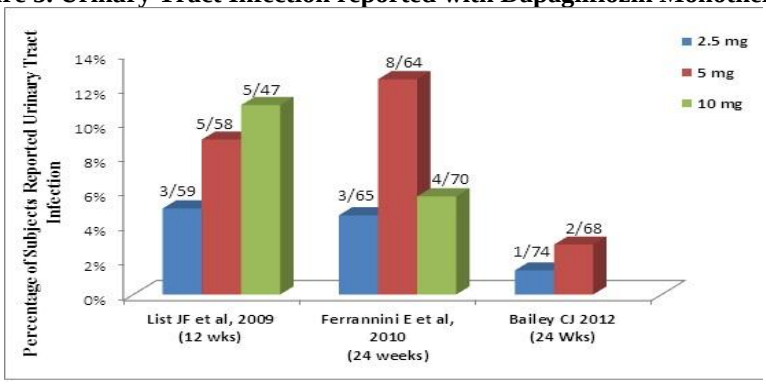


Figure 5. Urinary Tract Infection reported with Dapagliflozin Monotherapy



DISCUSSION

Hyperglycemia is a defining characteristic of type 2 diabetes mellitus. Management of type 2 diabetes mellitus (T2DM) remains complex and challenging. Although a wide range of pharmacotherapy for T2DM is available, many patients do not achieve glycemic targets, partly due to limiting side effects of current therapies, including weight gain, hypoglycemia, fluid retention and gastrointestinal side effects. Hence, the search for new treatment strategies is on-going. Improvement in glycemic control through inhibition of SGLT-2 is an attractive, insulin-independent target for increasing glucose excretion, and managing diabetes (Maurer TS *et al*., 2011; Idris I, Donnelly R, 2009; Chao EC, 2011). Therefore SGLT-2 inhibitors are considered to be potential antidiabetic drugs with a unique mechanism.

On 19 April 2012 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product dapagliflozin intended for the treatment of type 2 diabetes mellitus in adults. The benefits with dapagliflozin are its ability to lower blood glucose by increasing urinary glucose excretion. Dapagliflozin is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate due to intolerance and as add-on combination therapy in combination with other glucose-lowering medicinal products including insulin.

In placebo controlled clinical trials dapagliflozin at doses 10 and 20 mg once daily for 12 weeks in both early-stage and late-stage patients with T2DM and in drug-naive patients at doses 1, 2.5 or 5 mg daily for 24 weeks resulted in clinically significant improvements in glycaemic control and weight reduction (Zhang L *et al.*, 2010; Bailey CJ *et al.*, 2012). Dapagliflozin has demonstrated sustained, dose-dependent glucosuria over 24 hours with once-daily dosing in clinical trials (Neumiller JJ, 2010). Most efficacy outcomes appeared to be dose related without a proportional increase in AEs at the higher doses. These results align with trials evaluating higher doses of dapagliflozin, suggesting that efficacy can be greater with higher doses without compromising safety (Bailey CJ *et al.*, 2012).

Dapagliflozin plus metformin treatment resulted in significant improvement in glycaemic control, HbA_{1C} decrease from baseline ranged from -0.65 to -2.05% for 5 mg and -0.59 to 1.98% for 10 mg group and FPG decrease from baseline was -1.4 to -3.39 mmol/l for 5 mg and -0.52 to -3.39 for 10 mg group. In combination with pioglitazone, HbA_{1C} decrease from baseline ranged from -0.82 to -0.97% and FPG decrease from baseline ranged from -1.38 to -1.64 mmol/l respectively. Dapagliflozin at doses ranges from 5-10 mg/day in combination with glimepiride HbA_{1C} decrease from baseline was from -0.58 to -0.82% and FPG decrease from baseline ranged from -0.93 to -1.58 mmol/l. Addition of dapagliflozin to metformin has also been suggested as a new combination therapeutic option for treatment of T2DM. Dapagliflozin is expected to improve the treatment of type 2 diabetes as monotherapy or in combination with other oral or parenteral agents (Salvatore T *et al.*, 2011) and offer a new fundamentally different approach for treatment of diabetes (Washburn WN, 2012).

The incidence of AEs after single and multiple doses of dapagliflozin did not appear to be dose-related in clinical trials (Komoroski B *et al.*, 2009a). Multiple oral doses of 5, 25, and 100 mg dapagliflozin either alone or with metformin were found to be safe and well tolerated. The most common side effects are hypoglycaemia (when used with a sulphonylurea or insulin), urinary tract infection, genital tract infection, dyslipidaemia, dysuria and polyuria. The limited data available in patients > 75

years old, the use in patients at risk of volume depletion; hypotension and electrolytes imbalances are under evaluation. Dapagliflozin had no effect on markers of bone formation and resorption or BMD in both male and post-menopausal female T2DM patients (Ljunggren Ö *et al*., 2012). Studies to date have generally found dapagliflozin to be safe and well tolerated (Neumiller JJ, 2010).

There have been a specific safety issues regarding a tumour imbalance in dapagliflozin treated patients. The relative risk associated with dapagliflozin was above 1 for some tumours (bladder, prostate, breast) and below 1 for others (e.g. blood and lymphatic, ovary, renal tract), not resulting in an overall increased tumour risk associated with dapagliflozin (Strojek K *et al.*, 2011). The mechanism of action of dapagliflozin has no known link to tumor risk; however, long-term surveillance will be required to exclude any potential association (Wilding JP *et al*., 2012). In conclusion, dapagliflozin, with its unique and complementary mechanism of action, appears to be an important addition to the therapeutic options for the management of type 2 diabetes (Plosker GL, 2012).

DISCLOSURE OF INTEREST

The authors declare that they have no conflicts of interest concerning this article.

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